22. A composition according to claim 19, wherein the allergen or allergen extract is selected from the group consisting of pollen and food.

23. A composition according to claim 22, wherein the allergen or allergen extract is selected from the group consisting of grass pollen and ovalbumen.

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For the Examiner's convenience, the pending claims upon entry of this amendment are listed in Appendix B.

REMARKS

INTRODUCTORY COMMENTS:

In response to a request for continued examination under 37 CFR §1.114, the Examiner has withdrawn the finality of the previous Office Action and entered applicants' amendments. Thus, claims 1, 2, and 6-8 are currently pending. While the Examiner has withdrawn the enablement and indefiniteness rejections under 35 U.S.C. §112, first and second paragraphs, respectively, the Examiner has nevertheless again rejected the claims as follows:

1. Under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey that the inventor had possession of the claimed subject matter at the time of filing; and

2. Under 35 U.S.C. §103(a) as obvious over PCT Publication WO 96/34626, in view of PCT Publication WO 92/16556 and U.S. Patent No. 5,795,862 to Frank et al.

The rejections are addressed in part by the present amendments and in part by the following remarks.

THE AMENDMENTS:

Claim 1 has been amended to clarify the inventive subject matter by deleting "optionally modified by reaction with a cross-linking agent." In addition, claim 1 has been amended to recite that the claimed composition is capable of selectively enhancing a TH_1 response ***over a TH_2 response***. This is supported on page 1, lines 17-19, and on page 6, lines 15-23. All other elements of the claim are found in the originally submitted claims and throughout the

specification as filed. Since deletion of the "optional" terminology does not alter the scope of the claim, no new matter has been introduced by way of this amendment.

Similarly, claims 2 and 6-8 have been amended so that the terminology recited in these claims parallels that used in claim 1. As discussed in applicants' response to the Office Action dated July 5, 2001 (paper 9), this terminology is supported by the application as filed on page 1, lines 8-31, page 2, lines 9-14, and in Preparation 1 on page 4 of the specification. Accordingly, no new matter has been entered.

New claims 15-17 have been added to set forth that the allergen or allergen extract may be modified by reaction with a cross-linking agent such as glutaraldehyde. These claims find support on page 2, lines 15-16, of the specification. New claim 18 has been added to set forth the allergen or allergen extract need not be modified. This claim, too, is supported on page 2, lines 15-16. As pointed out by the Examiner in the Office Action under reply on page 2, item 5, second paragraph, "the term 'optionally' implies that [the] allergen needs not be modified."

New claims 19-23 have been introduced to set forth various examples of allergens and allergen extracts. This is supported on page 2, lines 9-14, and on page 4, lines 4-35 of the specification.

Thus, no new matter has been introduced by way of any of the above amendments, and entry thereof is proper and requested. Upon entry of this amendment, claims 1, 2, 6-8, and 15-23 are pending.

THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, REGARDING THE WRITTEN DESCRIPTION:

The Examiner has rejected all claims under 35 U.S.C. §112, first paragraph, as failing to satisfy the written description requirement. That is, the Examiner states that the pending claims contain matter that is not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventor had possession of the claimed invention when the application was filed. In addition, the Examiner directs applicants to the Revised Interim Guidelines for the Examination of Patent Applications Under 35 U.S.C. §112, ¶1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 (the "Guidelines").

Applicants have reviewed the Guidelines but are not entirely clear as to the Examiner's reasoning. Nevertheless, applicants note that the Examiner states that the specification discloses

only one modified allergen and one unmodified allergen. In addition, the Examiner appears to takes issue with the term "optionally" and states that there is an "indefinite number of undisclosed modified or unmodified allergens for a pharmaceutical composition." Furthermore, the Examiner characterizes the specification as failing "to provide a representative number of species to describe the [claimed] genus." Thus, ***it appears that the Examiner is asserting that the disclosure contained in the application, as filed, is insufficient to support the scope of the pending claims***. If this is ***not*** the case, applicants respectfully request that the Examiner disregard applicants' comments relating to this rejection and telephone the undersigned attorney for clarification of the rejection.

As an initial matter, applicants have deleted the term "optionally" from the claims to address the Examiner's apparent objection to the term and to clarify the inventive subject matter. As a result, independent claim 1 and all claims depending therefrom are directed to a pharmaceutical composition capable of selectively enhancing a TH_1 response comprising three elements: (1) tyrosine; (2) an allergen or allergen extract; and (3) 3-DMPL. Since the Examiner has not taken issue with the sufficiency of support for elements (1) and (3), the only remaining issue is whether the application, as filed, provides sufficient description of allergens to support the scope of the claims.

Upon review of the Guidelines on page 1105, center column, it is evident that the Examiner has the initial burden of overcoming a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. In addition, it is set forth on page 1106, right column, that the actual reduction to practice of a single species may adequately support a claim directed to an entire genus in a predictable art. Here, the specification discloses the actual reduction to practice of an exemplary modified allergen (Preparation 1 on page 4) as well as an exemplary unmodified allergen (Preparation 2 on page 4) In addition, applicants are willing to provide additional evidence of such actual reduction to practice in the form of a declaration if needed. Thus, the Examiner must demonstrate that the claims are directed to an invention in an unpredictable art in order to overcome the above-described presumption. As set forth in the Guidelines on page 1107, middle column: "A general allegation of 'unpredictability in the art' is not sufficient reason to support a rejection for lack of adequate written description." So far, the Examiner has presented ***no evidence*** regarding the predictability (or unpredictability) of the art and has therefore failed to overcome the presumption of the adequacy of support.

Applicants further submit that the specification provides many exemplary species of allergens and allergen extracts to describe the claimed genus. Upon review of the new dependent claims and the sections of the specification that provide support for these new claims, it should become abundantly clear that the inventive subject matter as claimed is commensurate with the disclosure contained in the specification. For example, claim 19 recites seven distinct sources from which the allergen or allergen extract may be derived. One such source is pollen, and claims 20 and 23 set forth three types of pollen. Another such source is house dust mite, and claim 21 recites two species of dust mites. Additional allergens are discussed on page 2, lines 12-14. Notably, it is disclosed on page 2, lines 11-12, that the term "allergen" includes a mixture of allergens from one or more sources. From a straightforward arithmetic calculation, then, it should be evident that claim 19 alone sets forth at least 120 different allergen mixtures. In combination with additional disclosure contained in the specification, 120 exemplary allergen mixtures provide ample support for the scope of independent claim 1.

Applicants therefore disagree with the Examiner's assertion: "The specification discloses only one modified allergen, that is, glutaraldehyde modified grass pollen extract." As discussed above, numerous exemplary allergens are disclosed in the application as filed. The specification also expressly discloses on page 2, lines 15-16 that dialdehyde is an exemplary class of cross-linking agent suitable for the practice of the invention and that glutaraldehyde is a member of that class. Thus, applicants again submit that it would be readily appreciated by one of ordinary skill in the art that any suitable cross-linking agent would suffice.

Accordingly, the application as filed fully supports the scope of the pending claims, and applicants respectfully request reconsideration and withdrawal of the rejection.

THE REJECTION UNDER 35 U.S.C. §103(a):

The Examiner has maintained the rejection of all claims as obvious over the teaching of WO 96/34626 in view of WO 92/16556 and U.S. Patent No. 5,795,862 to Frank et al. In the Office Action under reply, the Examiner reiterates her previous position and contends that applicants misapplied the test for obviousness. The Examiner states that the combination of these teachings renders the pending claims obvious.

Applicants again disagree for the reasons set forth in the Amendment Under 37 C.F.R. §1.116 submitted on February 19, 2002. In addition, applicants point out that *prima facie* obviousness requires a determination whether the claimed invention ***as a whole*** would have been

obvious over the cited art. MPEP 2141.02. Thus, *prima facie* obvious requires that the cited art teach or suggest ***all*** claim limitations. "All words in a claim must be considered in judging the patentablility of that claim against the prior art." MPEP 2143.03. In addition, it is provided in MPEP 2141.02: "Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." *See also In re Rijckaert,* 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). In this instance, the Examiner has erred by failing to take into account that the inventive composition ***selectively*** enhances a TH_1 response. That is, the inventive composition does not serve only to enhance a TH_1 response; the inventive composition ***selectively*** enhances a TH_1 response over a TH_2 response.

While not wishing to acquiesce in the Examiner's rejection, applicants have amended the claims to clarify the nonobvious nature of inventive composition. Thus, all pending claims are directed to a pharmaceutical composition capable of ***selectively enhancing a TH_1 response over a TH_2 response.*** Because such selective enhancement was not known in the art at the time the invention was made, applicants submit that the criteria to establish *prima facie* obviousness have not been met because none of the cited references suggests this feature. Applicants further note that nonobviousness may be established through evidence presented in the specification and by declaration from those of ordinary skill in the art.

As an initial matter, applicants point out that the Examiner is mistaken in stating that Frank et al. discloses 3-DMPL. While Frank et al. discloses a "Ribi adjuvant" and that 3-DMPL is available from Ribi ImmunoChem (now part of Corixa Corporation), one skilled in the art would recognize that Ribi ImmunoChem supplies many different types of chemicals, including a number of adjuvants other than 3-DMPL. Thus, Frank et al. does not disclose 3-DMPL and is not relevant to the invention as claimed. In addition, the Examiner has stated that the specification on page 4 requires that the allergen be chemically modified. This is simply untrue, as evidenced by Preparation 2 described on page 4.

Applicants further point out that, as discussed in applicant's previous response, allergy is due, in part, to an imbalance of the immune system in which there is a predominance of allergen specific TH_2 cells over TH_1 cells leading to abnormally high IgE antibody levels and inflammatory responses. Therefore, a goal of allergy treatment is not merely to enhance a TH_1 response, but to switch the abnormal T cell response of an allergic patient from a predominantly TH_2 driven response to a more pronounced TH_1 profile. Neither WO 92/16556 nor Frank et al.

suggests that formulations containing 3-DMPL would be able to switch the unbalanced predominantly TH_2 driven response of an allergic individual to a more pronounced TH_1 profile.

As set forth in the Example described on pages 4-6 of the application, there is clear evidence of unexpected results that establishes the nonobviousness of the present invention and thus distinguishes the invention over the cited art. As discussed in applicants' previous response, the results of experiments involving ovalbumin are tabulated on page 6 of the specification. The results show that the inventive formulation (1) induces much higher levels of IgG2 antibody responses and (2) does not significantly enhance the IgE response. As shown in the table on page 6, inventive formulation-induced IgG2 responses are ***about three orders of magnitude*** higher than the response induced by the other formulations. In addition, the IgE response for the inventive formulation is ***lower*** than the IgE response for the other formulations. In fact, the administration of the inventive formulation resulted in ***no significant change*** in the IgE level than normal mouse serum values of IgE. All state of the art formulations ***more than doubled*** the IgE value. As stated under the heading Biological Activity on page 5 of the specification, TH_1 inducing activity in mice can be equated with the production of IgG2a and IgG2b antibodies, while TH_2 inducing activity can be equated with the production of IgG1 and IgE antibodies. It is clear, then, that the inventive formulation's selective enhancement of a TH_1 response over a TH_2 response is a feature that is not suggested by the cited art. Absent knowledge of the present invention and following the Examiner's interpretation of the cited references, one of ordinary skill in the art would have expected that ***both*** TH_1 and TH_2 responses would be enhanced. One skilled in the art would not have expected that the TH_1 response is selectively enhanced over the TH_2 response.

In further support of the nonobvious nature of the invention as claimed, Applicants submit herewith a Declaration under 37 CFR §1.132 from Derek Richardson of Allergy Therapeutics Limited, that sets forth the nonobviousness of the invention, as supported by the unexpected results and the successful commercialization of the claimed invention. According to *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), commercial success may represent indicia of nonobviousness.

Therefore, applicants submit that the claimed invention is nonobvious over the cited references, based on both the failure of the Examiner to establish *prima facie* obviousness, on the unexpected result of the synergistic, selective TH_1 directing effect of tyrosine and 3-DMPL, and

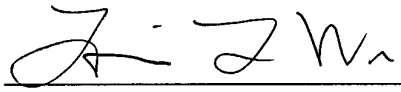
objective indicia of nonobviousness. Reconsideration of the rejection is warranted and respectfully requested.

CONCLUSION

For the foregoing reasons, applicants submit that the claims satisfy all requirements of 35 U.S.C. §112 and are patentable over the cited art. A Notice of Allowance is requested, and a prompt mailing thereof would be much appreciated.

The Examiner is requested to contact the undersigned attorney at (650) 330-4912 if there are any questions concerning this communication.

Respectfully submitted,

By: 

Louis L. Wu
Registration No. 44,413

REED & ASSOCIATES
800 Menlo Avenue, Suite 210
Menlo Park, California 94025
(650) 330-0900 Telephone
(650) 330-0980 Facsimile
F:\Document\9950\0002\Amendment 1.111 (11.27.02).DOC

APPENDIX A

REDACTIONS INDICATING AMENDMENTS MADE TO THE CLAIMS (UNDERLINING INDICATES ADDITION, ~~STRIKETHROUGH~~ INDICATES DELETION)

Please amend claims 1, 2, and 6-8, and add claims 15-23.

1. (Thrice Amended) A pharmaceutical composition capable of selectively enhancing a TH_1 response over a TH_2 response, comprising tyrosine, an allergen or allergen extract, ~~optionally modified by reaction with a cross-linking agent~~, and 3-DMPL.

2. (Amended) A composition according to claim 1, wherein the allergen or allergen extract is coated with and/or adsorbed onto tyrosine.

6. (Amended) A composition according to claim 2, wherein the allergen or allergen extract is coated with the tyrosine.

7. (Amended) A composition according to claim 2, wherein the allergen or allergen extract is adsorbed onto the tyrosine.

8. (Amended) A composition according to claim 2, wherein the allergen or allergen extract is coated with and adsorbed onto the tyrosine.

15. (New) A composition according to claim 1, wherein the allergen or allergen extract is modified by reaction with a cross-linking agent.

16. (New) A composition according to claim 15, wherein the cross-linking agent is a dialdehyde.

17. (New) A composition according to claim 16, wherein the dialdehyde is glutaraldehyde.

18. (New) A composition according to claim 1, wherein the allergen or allergen extract is not modified by reaction with a cross-linking agent.

19. (New) A composition according to claim 1, wherein the allergen or allergen extract is derived from a source selected from pollen, food, insect venom, mold, animal fur, house dust mite, and combinations thereof.

20. (New) A composition according to claim 19, wherein the allergen or allergen extract is derived from ragweed pollen or birch pollen.

21. (New) A composition according to claim 19, wherein the allergen or allergen extract is derived from dust mite of species *D. farinae* or *D.pteryssinus*.

22. (New) A composition according to claim 19, wherein the allergen or allergen extract is selected from the group consisting of pollen and food.

23. (New) A composition according to claim 22, wherein the allergen or allergen extract is selected from the group consisting of grass pollen and ovalbumen.